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Postpartum Acquired Factor VIII Inhibitors: Results of a Survey

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Postpartum factor VIII inhibitors are rare; thus, collecting clinical and treatment data may provide valuable information in guiding patient management. This paper reports the results of a survey of United States and Canadian hemophilia centers on 14 patients with postpartum acquired factor VIII inhibitors. Patients ranged in age from 23 to 40 years. Parity at diagnosis was most frequently the first gestation. Two patients were diagnosed prepartum, but two patients only up to one year postpartum. Initial inhibitor titers ranged from two to 550 Bethesda units (BU), and rose to five to 885 BU. The median duration of the inhibitor was 27 months, with two of the 14 inhibitors unresolved at the time of the survey. A total of 80 bleeding episodes occurred, five of which were life or limb threatening. Three patients received no blood products and were not hospitalized. Of those treated for hemostasis, activated prothrombin complex concentrates and porcine factor VIII were most often reported to be effective. For immunosuppression, all patients received steroids and most received additional treatment. Steroids were reported ineffective more frequently than cyclophosphamide. No adverse fetal events were noted and there was no maternal mortality. These results underline the clinical heterogeneity of the severity of postpartum factor VIII inhibitors, and provide treatment guidelines in the absence of prospective studies. Am. J. Hematol. 59:1–4, 1998.

Key words: acquired factor VIII inhibitor; postpartum

INTRODUCTION

Acquired factor VIII inhibitors in nonhemophiliacs is a rare but serious disorder, with significant associated morbidity and mortality [1]. This condition can occur in the postpartum state in a group of young patients who are otherwise well, thus, treatment decisions must be weighed very carefully. Due to the rare incidence of acquired factor VIII inhibitors, limited prospective randomized data are currently available to assess treatment outcomes [2]. A recent review has summarized a retrospective analysis of 51 previously published cases of postpartum factor VIII inhibitors [3]. The current study reports on 14 additional patients not previously published, except for one case in abstract form [4], and one case as part of a treatment trial [5]. This survey provides further insight into the natural history of postpartum factor VIII inhibitors, and may guide treatment decisions in the absence of prospective data.

METHODS

A standard questionnaire was mailed to Hemophilia Centers across Canada and the United States, as well as to physicians known to have used porcine factor VIII in the treatment of female patients with acquired factor VIII inhibitors. Ten centers have contributed information on a total of 14 patients as detailed below. Contributors outside the author's center are listed in the appendix. As not all questions were answered fully on all patients, data are presented as the total available answers given. Linear regression analysis was performed according to standard statistical methods.

RESULTS

Individual patient information is summarized in Table I and detailed below. The acquired factor VIII inhibitors of the fourteen patients were diagnosed between 1981

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TABLE I. Individual Patient Characteristics*

No.	Age	Parity	Time of diagnosis	First inhibitor titer (BU)	Highest inhibitor titer (BU)	Factor VIII level at diagnosis (%)	Number of bleeds	Duration of inhibitor (months)
01	34	5	prepartum	10.9	885	2.8	29	60[a]
02	37	2	<3 months	20	198	2.3	5	27
03	23	1	<3 months	11	295	<3	3	6[a]
04	28	2	<3 months	20	650	?	1	72
05	26	?	<3 months	39	39	1.8	1	36
06	32	1	<3 days	120	250	<1	4	84
07	23	1	6–12 months	189	189	<1	3	28
08	29	1	6–12 months	24	70	4	13	18
09	28	1	<3 months	550	550	1.4	8	131
10	30	1	<1 months	2	5	10	2	1
11	30	5	<3 days	2.8	9.5	5	3	6.5
12	40	1	<3 days	12	60	5	3	2
13	35	?	prepartum	?	14.4	6	1	2
14	35	1	<3 months	11	11	3	4	4
Median	30	1	<3 months	20	70	3	3	27

*BU, Bethesda units.
[a]Ongoing.

and 1995. Mean patient age was 30, ranging from 23 to 40 years. Acquisition of the inhibitor occurred with the first pregnancy in eight patients, and the second or subsequent pregnancies in four patients. Definitive diagnosis of an acquired factor VIII inhibitor was made prepartum in two of the patients, and within days of delivery in three cases. Seven patients were diagnosed within three months of delivery and two only at six to 12 months postpartum. Both of the latter patients had symptoms of a coagulopathy for several months preceding the actual diagnosis. Patient no. 7 had excess bruising starting within one month post delivery and patient no. 8 had a calf muscle hematoma within three months of delivery. Diagnosis in both cases was established upon referral to a tertiary care institution. At the time of presentation, one patient was on prednisone for muscle weakness and diplopia and the remainder of patients had no previous illnesses and were on no medications. The factor VIII inhibitor titers at diagnosis ranged from two to 550 Bethesda units (BU), with a median of 20 BU.

The incidence of bleeding ranged from a single episode in three patients to up to 29 documented bleeds in one case. The median number of bleeding events per patient was three. Bleeding was ranked as mild, moderate, severe, and life or limb threatening. An overall total of 80 bleeding events were reported, and of these, five were life or limb threatening, 34 severe, 33 moderate, and eight were considered mild. More than half the events were reported to be spontaneous. Forty-five of the bleeding episodes involved either intraarticular or intramuscular hemorrhage. Other serious bleeding events included postpartum hemorrhage, vaginal bleeding, retroperitoneal bleeding, and surgical bleeding associated with cesarian section and hysterectomy. Milder bleeding manifestations included hematuria, epitaxis, and ecchymoses. Two patients did not receive any blood products. At the other end of the spectrum, one patient required 48 units of packed red blood cells, 60 units of platelets, and also received cryoprecipitate, plasma, as well as plasma exchange. This patient had a massive postpartum hemorrhage necessitating a hysterectomy, which was complicated by an obstructing rectal wall hematoma. Much of the platelet plasma and cryoprecipitate was given in the setting of massive red blood cell transfusion. Blood product use and its effectiveness for hemostasis, as reported, are detailed in Table II. The use of antifibrinolytics is included in Table II as well. Antifibrinolytics were either used alone for mild bleeding episodes, or as adjuncts to other products for more serious symptoms. For control of bleeding, both activated prothrombin complex concentrates and porcine factor VIII were more often reported to be beneficial than replacement with human factor VIII. Prothrombin complex concentrates were used most frequently for control of hemostasis. Desmopression acetate (DDAVP) was given to two patients in an attempt to raise endogenous factor VIII levels, but was reported unsuccessful in both. No patient in this series received recombinant factor VIIa.

Along with transfusion of blood products to control bleeding, immunosuppressive therapy was commonly used to eradicate the inhibitor. All patients received steroids; seven were also treated with cyclophosphamide. Less frequently used treatments included intravenous immunoglobulin, azathioprim, cyclosporin A, plasmaphoresis and factor VIII infusion. Four patients were treated with steroids alone. The effectiveness of these treatments are listed in Table III. The duration of the inhibitor ranged from one to 131 months; median duration was 27 months. Two cases had ongoing inhibitors at 6-month and 5-year follow-up. No conclusive evaluation can be

TABLE II. Blood Product and Antifibrinolytic Use and Evaluation of Response*

Product	Number of patients/bleeding events treated	Best hemostatic response for each patient[a]
Packed red blood cells	8/11	NA
Human factor VIII	6/7	?,1,1,1,3,4
Prothrombin complex concentrate	2/3	?,1
Activated prothrombin complex concentrate	7/32	?,?,3,3,3,4,4
Porcine factor VIII	6/7	?,3,3,3,4,4
Platelets	1/2	?
Cryoprecipitate	2/2	?
Plasma	4/5	?
Antifibrinolytic	5/8	?,?,2,2,2

*NA, not applicable.
[a]1, no improvement; 2, possible benefit; 3, probable benefit; 4, clear benefit.

TABLE III. Immunosuppression and Evaluation of Response

Agent	Number of patients treated	Best response[a]
Steroids	14	?,?,?,?,1,1,1,1,1,2,2,3,4,4
Cyclophosphamide	7	?,1,2,3,3,3,3
Intravenous immunoglobulin	5	?,1,2,3,4
Azathioprim	3	?,?,4
Cyclosporin A	1	4
Plasmapheresis	1	4
Factor VIII	1	1

[a]1, no improvement; 2, possible benefit; 3, probable benefit; 4, clear benefit.

made on the effect of treatment type and duration of the inhibitor because of the relatively small number of patients in each group, and because not all treatment modalities were started at the time of diagnosis. It is of note that the three patients with the shortest duration of inhibitor were given either cyclophosphamide or cyclosporin A. As rated by the treating center, steroids were found to be ineffective more frequently than cyclophosphamide.

Linear regression analysis showed a correlation between the highest inhibitor titer against factor VIII, and the duration of the inhibitor ($r = 0.67$). The highest titer of inhibitor also correlated with the number of bleeding events per patient ($r = 0.60$). No correlation was evident, however, between the number of bleeding episodes and the duration of the inhibitor. The highest titer of factor VIII inhibitor measured ranged from five to 885 BU, with a median of 70 BU. Seven patients had an anamnestic response to treatment.

Two minor treatment-related adverse events were noted: one episode of chills, tremor, and back pain following intravenous immunoglobulin; and one episode of neck and back pain with the use of porcine factor VIII. Three patients did not need to be hospitalized during the course of their illness. Those requiring hospitalization stayed from 12 to 50 days, with a median stay of 18 days. Fetal outcome was not adversely affected in any of these patients. Three patients are known to have had six subsequent pregnancies, four with an anamnestic response of the inhibitor, and two without evidence of an inhibitor.

DISCUSSION

This series of patients with postpartum acquired factor VIII inhibitors demonstrate the heterogeneity of the natural history of this condition. Fatalities have been reported in the literature [3,6], but were not found in the current series. Twelve of the fourteen inhibitors had resolved at the time of the survey, and three patients required no hospitalization; two patients had no blood product support during their illness. Although five of the 80 bleeding episodes were considered limb or life threatening, half of the bleeding events were mild or moderate in nature. Acquired factor VIII inhibitors were diagnosed both after the first, or subsequent gestations. This disorder thus appears to be self-limited, and in a minority of cases, does not result in clinically significant morbidity. Diagnosis of the inhibitor was delayed up to one year postpartum in two of the cases. One can presume that minimally symptomatic patients may at times remain undiagnosed.

Comparison of the current series of patients to cases previously published between 1937 and 1993 and reviewed by Hauser et al. [3] lead to some interesting observations. The 51 patients Hauser et al. reviewed had a 76% complete response rate at the time of observation, and three fatalities. A total of 122 bleeding episodes were noted in the 51 cases. The highest level of inhibitor recorded had a median value of 20 BU. Ten of their patients did not receive any immunosuppressive treatment; 23 were given steroids alone. The current series, in comparison, had a compete response rate of 85% at the time of observation and no fatalities. This outcome occurred despite a relatively higher number of bleeding episodes and a reported higher maximal inhibitor titer. All of the current patients were treated with prednisone, and 10 of the 14 women were given additional immunosuppression. These data suggest that the increased use of immunosuppressive therapy may account for the more favorable outcome observed. It would also suggest that treatment should be administered by hemophilia treatment centers experienced in the treatment of this condition.

Hemostatic response in this series was most reliably achieved with either activated prothrombin complex concentrates or porcine factor VIII. Both treatments are known to be effective in acquired hemophilia in general [7,8]. Although DDAVP was ineffective in this group of patients, it has reported benefit, particularly in those with low level inhibitors [9]. Recombinant factor VIIa has

also recently been used successfully in the postpartum setting [10].

Consistent with previously published observations on the immunosuppressive treatment of postpartum inhibitors [3] and acquired inhibitors in general [2], additional benefit is obtained by the use of cyclophosphamide either with, or following steroid use. The use of cyclophosphamide should thus be considered in cases of steroid failure. Other immunosuppressants, including azathioprim, cyclosporin A, and intravenous immunoglobulin were used less frequently, but appear effective as well. Short-term side effects were minimal; however, long term sequelae are unknown.

Fetal outcome was favorable in this series; however, serious morbidity has been reported in an infant with transplacentally acquired factor VIII inhibitor [11]. When the diagnosis of a factor VIII inhibitor is known prepartum, the mode of delivery should be carefully assessed. Further studies, particularly on the immunobiological aspects of this challenging disease, are needed to advance our understanding of postpartum factor VIII inhibitors.

REFERENCES

1. Green D, Lechner K: A survey of 215 non-hemophilic patients with inhibitors to factor VIII. Thromb Haemost 45:200, 1981.
2. Green D, Rademaker AW, Briet E: A prospective randomized trial of prednisone and cyclophosphamide in the treatment of patients with factor VIII autoantibodies. Thromb Haemost 70:753, 1993.
3. Hauser I, Schneider B, Lechner K: Post-partum factor VIII inhibitors. A review of the literature with special reference to the value of steroid and immunosuppressive treatment. Thromb Haemost 73:1, 1995.
4. Brox A, Laryea H, Pelletier M: The treatment of acquired factor VIII inhibitors with cyclosporine. Blood 88:36a, 1996.
5. Schwartz RS, Gabriel DA, Aledort LM, Green D, Kessler CM: A prospective study of treatment of acquired (autoimmune) factor VIII inhibitors with high-dose intravenous gammaglobulin. Blood 86:797, 1995.
6. Haedicke G, O'Sullivan J, Seidler C, Donat W, Crowley JP: Tracheal obstruction after emergency tracheostomy in a patient with a postpartum factor VIII inhibitor. Crit Care Med 18:449, 1990.
7. Kasper CK: Treatment of factor VIII inhibitors. Prog Hemostasis Thromb 9:57, 1989.
8. Morrison AE, Ludlam CA, Kessler C: Use of porcine factor VIII in the treatment of patients with acquired hemophilia. Blood 81:1513, 1993.
9. Mudad R, Kane WH: DDAVP in acquired hemophilia A: Case report and review of the literature. Am J Hematol 43:295, 1993.
10. Meili EO, Dazzi H, Von Felten A: Recombinant activated factor VII (Novosen Novo Nordisk) for hemostasis in acquired factor VIII-inhibitor hemophilia. Schweiz Med Wochenschr 125:405, 1995.
11. Ries M, Wolfel D, Maier-Brandt B: Severe intracranial hemorrhage in a newborn infant with transplacental transfer of an acquired factor VIII:C inhibitor. J Pediatr 127:649, 1995.

APPENDIX

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